REMARKS

In the Office Action dated March 27, 2007, claims 37-45 and 47-50 are pending in the application.[1] Claims 41 and 45 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 38-41, 44-45 and 48-50 are rejected as allegedly lacking enabling and descriptive support. Furthermore, Claims 38, 44, 45 and 48 under 35 U.S.C. §102(b) as allegedly anticipated by Kiyoshi et al. (U.S. patent No. 5,453,491).

A telephone interview was conducted with Examiner Basi on August 14, 2007. Applicants, through the undersigned, wish to thank Examiner Basi for the courtesy and assistance extended on behalf of Applicants during the interview.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the first instance, Applicants direct the Examiner's attention to the amendments to the claims. Claim 38 has been amended to delete the term "part". Claim 41 has been amended to correct a typographical error. No new matter is introduced by the forgoing amendments.

With respect to the rejection under 35 U.S.C. §112, second paragraph, the Examiner states that amended claim 41 is indefinite because the claim depends on cancelled claim 30. Applicants have amended claim 41 to depend on claims 38 and 40. Claim 41, as amended, is not indefinite.

In addition, the Examiner maintains that the terms "mature form" and "soluble form" are indefinite. Applicants previously submitted that the term represents a form of the NR4 polypeptide that is different in length from the newly translated NR4 polypeptide as a result of

post-translational processing. Applicants also submitted Exhibits 1-6, which demonstrate that the basic structure of haemopoietin receptors and methods for predicting the site of cleavage between a signal sequence and the mature protein were known prior to the present invention. Therefore, Applicants established that based on the information provided in the specification, those skilled in the art would be able to make a reasonable determination of the starting and ending amino acid residues of a "mature form" or "soluble form" of NR4. Therefore, Applicants concluded that a "soluble form" and a "mature form" of human NR4 are sufficiently defined in the specification, despite the absence of a specific disclosure of the precise starting and ending amino acid residues of the respective forms.

However, the Examiner has maintained the rejection, alleging that neither the specification nor the art defines the term "soluble form" or "mature form." The Examiner is of the opinion that even if methods known in the art were used to study the structure of the claimed protein, the methods would not necessarily all give the same answer as to structure of the "soluble form" or "mature form." The Examiner contends that there is still ambiguity as to the exact nature of the "soluble form" and "mature form".

Applicants respectfully submit that Example 6 of the specification (page 37) and Figure 1 define the various domains of murine NR4 including a signal sequence, an extracellular domain, a transmembrane domain, and a cytoplasmic domain. The specification further identifies at page 32, line 25-26, that "A26 or T27" is the predicted first amino acid of the murine "mature protein". Additionally, the specification demonstrates the production of a "soluble" murine NR4 polypeptide (pages 40-41, Example 12). Moreover, the specification discloses in Example 11 (pages 39-40) that SEQ ID NO: 4 is the human homolog of murine R4

[1] On the Office Action Summary sheet, the Examiner mistakenly states that Claims 37-45, 47 and 50 are pending.

with 75% similarity at the amino acid level; and Figure 7 aligns the human sequence with the murine sequence. Applicants respectfully submit that this detailed description of the murine NR4 protein (IL-13 receptor alpha chain) in the specification clearly demonstrates that appropriate means were available in 1995/1996 to one skilled in the art to determine the signal sequence and trans-membrane regions of a protein. Through these means, coupled with the instant disclosure of the murine mature and soluble forms, and the comparison between the murine and human protein sequences, those skilled in the art would have been able to readily determine the signal sequence and trans-membrane regions of the human NR4 protein, thereby determining the structures of the soluble and mature forms of the human NR4 protein, at the time the present application was filed.

In this connection, Applicants respectfully direct the Examiner's attention to **Exhibits 1-6** submitted in Applicants' pervious Response, which further support the notion that methods and techniques were available to those skilled in the art for determining the signal peptide and transmembrane regions (and therefore the mature and soluble forms) of proteins.

Applicants provide herewith another publication, Milouex et al., *FEBS Letters* 401: 163-166 (1997) (attached hereto as **Exhibit A**), which describes methods for determining the signal sequence cleavage position and the transmembrane region of human IL-13Rα, and further discloses the sequences of the soluble (containing the extracellular domain) and mature forms of human IL-13Rα. It is noted that the signal sequence of human IL-13Rα predicted in the Milouex reference (Figure 1) is consistent with the murine signal sequence proposed in the present application.

Applicants further respectfully submit that the Milouex reference, although published after the priority date of the present application, provides additional support for the notion that appropriate means were available at the relevant time for one skilled in the art to determine the signal sequence and trans-membrane regions of a protein. Applicants respectfully submit that the Examiner has not provided any basis for the allegation that the methods available at the time would not give the same answer as to structure of the "soluble form" or "mature form". Applicants respectfully submit that all the methods available at the time would have provided consistent information as to structures of the "soluble form" and the "mature form".

Applicants intend to submit a §1.132 Declaration to provide additional support for Applicants' position.

Accordingly, Applicants respectfully submit that a "soluble form" and a "mature form" of human NR4 are sufficiently defined in the specification, despite the absence of a specific disclosure of the precise starting and ending amino acid residues of the respective forms.

In view of the foregoing, Applicants respectfully submit that the rejection under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 38-41, 44-45 and 48-50 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the enablement requirement. Claims 38, 41, 44-45, and 48-50 are separately rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the

written description requirement. The Examiner's principal concern appears to be directed to the recitation of "a part or fragment of SEQ ID NO: 4" in independent claim 38.

In the first instance, Applicants respectfully submit that claim 38 has been amended to delete the term "part". Applicants further submit that the specification does provide guidance for "fragments" of NR4. For example, Example 6 of the specification (page 37 and Figure 1) defines the various domains of murine NR4 including a signal sequence, an extracellular domain, a transmembrane domain, and a cytoplasmic domain. Example 11 (pages 39-40) discloses that SEQ ID NO: 4 is the human homolog of murine NR4 with 75% similarity at the amino acid level; and Figure 7 aligns the human sequence with the murine sequence.

Additionally, as submitted above, the specification provides adequate disclosure that supports a soluble form and a mature protein of NR4, both of which are fragments of the NR4 proteins. Applicants respectfully submit that the rejections should be withdrawn at least in respect to claims 39-41 and 45.

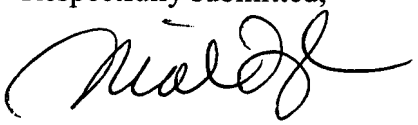
In view of the disclosure in the specification, Applicants respectfully submit that the term "fragment" of SEQ ID NO: 4, including a soluble and a mature fragment of SEQ ID NO: 4, is fully supported by the specification. As such, the enablement and written description rejections under 35 U.S.C. §112, first paragraph, are overcome. Withdrawal of the rejections is respectfully requested.

Claims 38, 44-45 and 48 are rejected under 35 U.S.C. §102(b) as anticipated by Kiyoshi et al. (U.S. Patent No. 5,453,491). The rejection is apparently based on the Examiner's interpretation of the term "a part or fragment" of SEQ ID NO: 4 as reading on an amino acid, which is disclosed by Kiyoshi et al.

Applicants respectfully submit that the term "part" has been deleted from claim 38. Claim 38, as amended, recites "a fragment" of SEQ ID NO: 4. Applicants respectfully submit that the term "fragment" of a protein is routinely used in the field and would not be understood by anyone skilled in the art to mean one amino acid. A fragment is understood to include at least a chain of several amino acids. Therefore, Applicants respectfully submit that Kiyoshi et al. do not teach a fragment of SEQ ID NO: 4 as claimed. Accordingly, the §102(b) rejection based on Kiyoshi et al. is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Encl.: Exhibit A

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FEBS Letters 401 (1997) 163–166

Cloning of the human IL-13Rα1 chain and reconstitution with the IL-4Rα of a functional IL-4/IL-13 receptor complex

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Abstract **The human homologue of the recently cloned murine IL-13 binding protein (IL-13Rα1) was cloned from a cDNA library derived from the carcinoma cell line CAKI-1. The cloned cDNA encodes a 427 amino acid protein with two consensus patterns characteristic of the hematopoietic cytokine receptor family and a short cytoplasmic tail. The human protein is 74% identical to the murine IL-13Rα1, and 27% identical to the human IL-13Rα2. CHO cells expressing recombinant hIL-13Rα1 specifically bind IL-13 ($K_d \approx 4$ nM) but not IL-4. Co-expression of the cloned cDNA with that of IL-4Rα resulted in a receptor complex that displayed high affinity for IL-13 ($K_d \approx 30$ pM), and that allowed cross-competition of IL-13 and IL-4. Electrophoretic mobility shift assay showed that IL-13 and IL-4 were able to activate Stat6 in cells expressing both IL-4Rα and IL-13Rα1, while no activation was observed in cells expressing either one or the other alone.**

Key words: IL-13 binding protein; IL-13 signal transduction; IL-4 receptor complex

1. Introduction

Interleukin-13 (IL-13) is a cytokine secreted by activated T-lymphocytes which regulates inflammatory and immune responses [1,2]. It shares several biological activities with IL-4, another T-cell derived cytokine, in a variety of cell types such as B-cells, monocytes, fibroblasts and endothelial cells [3].

The functional redundancy of IL-4 and IL-13 suggested very early on that both cytokines probably shared receptor components [4–6]. The IL-4 receptor comprises two chains, the IL-4Rα and the γc [7–10]. Neither of these two chains binds IL-13 [5], but recent reports have shown that IL-4Rα contributes to the IL-13 receptor [11–13].

Recently, two proteins that bind specifically IL-13 have been cloned, one from murine tissue [14] and the other from human cells [15]. Since both proteins are most probably responsible for the initial interaction of IL-13 with the receptor complex(es) we propose to call them IL-13Rα1 and IL-13Rα2. IL-13Rα1 and IL-13Rα2 are distantly related (27% identity and 46% homology), but both proteins have short cytoplasmic domains, and two consensus patterns, four conserved cysteines in the amino-terminal half of the extra cellular domain and the WSXWS motif located in the C-terminal region of the extra cellular domain, considered signatures of the hematopoietic cytokine receptor family (for review see [19]). Interestingly, both proteins bind IL-13 with very different affinities, $K_d \approx 10$ nM and 50 pM for IL-13Rα1 and IL-13Rα2, respectively. We describe here the cloning of the human IL-13Rα1, and the pharmacological and functional characterization of the recombinant protein expressed alone or with IL-4Rα in stably transfected CHO cells.

2. Materials and methods

2.1. Growth factors and cells

Recombinant hIL-13 was produced and purified in our laboratory as previously described [2]. Human IL-4 was obtained from Tebu (Le Perray en Yvelines, France).

CAKI-1 cells (ATCC HTB 46), the B9 hybridoma cell line, and CHO cells were cultured as described [15].

2.2. cDNA library construction, isolation of cDNAs and sequence analysis

Total RNA from B9 hybridoma cells was used to synthesize cDNA [2]. A specific DNA fragment of the murine IL-13Rα1 was obtained by PCR using this cDNA and the following primers: 5'-AGAGGAATTACCCCTGGATG-3' (sense) and 5'-TCAAGGAGCTGCTGCTTTCTTCA-3' (anti-sense) corresponding to the nucleotides 249–268 and 1256–1275, respectively, of the mIL-13Rα1 sequence described by Hilton et al. [14].

The PCR product obtained (1027 bp) was purified, labelled (specific activity 2.4×10^9 dpm/μg) using the Random Primers DNA labelling kit (BRL), and used as a probe to screen a CAKI-1 cDNA library [15].

2.3. Binding and biological activity assays

Binding experiments on transfected CHO cells were performed using radiolabelled hIL-13 as described [5].

For the electrophoretic mobility shift assay (EMSA), 2×10^6 CHO cells or recombinant cell lines were plated onto 10 cm dishes and transfected 24 h later with 6 μg of plasmid DNA. After 48 h, the cells were washed and incubated in the presence of hIL-13 or hIL-4 (10 nM) for 30 min at 37°C, then rinsed twice with cold PBS containing 0.5 mM EDTA, harvested with a cell scraper in 1.2 ml PBS and finally transferred into 1.5 ml microcentrifuge tubes. Cellular extracts were prepared as described by Jiang and Eberhardt [16]. Gel shift assays were performed as described by Kölher et al. [17] with 10–20 μg of proteins and 5×10^4–1×10^5 cpm of the ^{32}P-labelled probe corresponding to the human Cε element from the human Cε control region [18] (5'-GATCCACTTCCCAAGAACAGA-3', the core sequence is underlined). Stat6 containing complexes were confirmed by supershifting with 2 μg of a monoclonal antibody anti-Stat6, M20 (Santa Cruz, CA), added to the binding reaction before EMSA.

3. Results

3.1. Cloning and sequencing of the human IL-13Rα1

A DNA fragment of the murine IL-13Rα1 [14] was derived from B9 total RNA and used to screen by hybridization a CAKI-1 cDNA library. Homologous sequences were relatively abundant (1/5000). The homologous full length cDNA is 3999 bases long, excluding the poly-A tract, and has a long 3' untranslated region of 2145 bases. A canonical AATAAA polyadenylation signal is found at the predicted location. The open reading frame between nucleotides 34 and 1851 defines a

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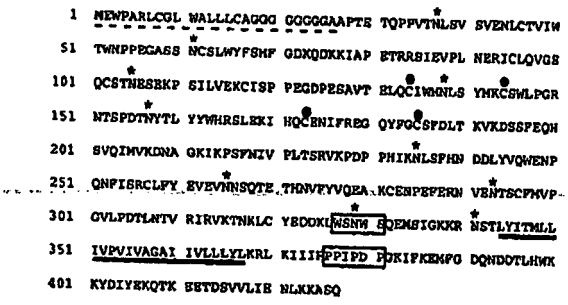

Fig. 1. Amino acid sequence of human IL-13Rα1. The amino acids corresponding to the predicted signal peptide are indicated with dashes. Potential *N*-glycosylation sites (Asn-X-Ser/Thr) are labelled with asterisks. Conserved cysteines in the hematopoietic cytokine receptor family are labelled with solid circles. The WSXWS and PXXPXP motifs are boxed. And the transmembrane domain is underlined. The human IL-13Rα1 cDNA sequence has been submitted to the EMBL Data Library (accession number Y09328).

polypeptide of 427 amino acids. The sequence codes for a membrane protein with a putative signal peptide, a single membrane-spanning domain and a short cytoplasmic tail (Fig. 1). Ten sites for potential N-linked glycosylation are located in the extracellular region. Importantly, two consensus patterns considered signatures of the hematopoietic cytokine receptor family (for review see [19]) are also found, four conserved cysteines in the amino-terminal half of the extra cellular domain, and the WSXWS motif located in the C-terminal region of the extra cellular domain. Furthermore, a proline-rich motif (PXXPXP) is located in the cytoplasmic region near the transmembrane domain. Alignment studies reveal homologies with the murine IL-13Rα1 (74% identity and 84% similarity) and to a lesser extent with the human IL-13Rα2 (27% identity and 51% similarity) and with the human IL-5Rα (26% identity and 46% similarity).

3.2. Expression and characterization of the IL-13 binding protein

CHO cells transfected with the isolated cDNA encoding the IL-13Rα1 showed specific binding of labelled IL-13. Scatchard analysis of the saturation curve showed a single component site with a K_d value of 4.5 ± 0.5 nM and a maximal binding capacity of 2.6×10^4 receptors/cell (Fig. 2A). The affinity displayed by the recombinant receptor is much lower than that displayed by the IL-13Rα2, with a K_d of 57 ± 10 pM [15]. However, when the saturation experiments were performed on CHO cells co-expressing IL-13Rα1 with IL-4Rα, the Scatchard analysis clearly showed the presence of two sites for IL-13 (Fig. 2B). One exhibited a dramatic increase in affinity (K_d: 32 ± 8 pM), and the other had a K_d similar to the one observed in the cells expressing IL-13Rα1 alone, 4.2 ± 1.4 nM. The high affinity binding site was not detected if the saturation experiments were performed in the presence of a large excess of IL-4 (not shown). No modification in IL-13 affinity resulted from the co-expression of IL-13Rα1 and IL-13Rα2 (not shown) and IL-13 did not bind to IL-4Rα, as previously described [5].

In competition studies, IL-13 was effective in inhibiting the labelled IL-13 binding to the cells expressing the IL-13Rα1. Labelled IL-4 neither bound to the IL-13Rα1, nor inhibited the binding of labelled IL-13 to this receptor (Fig. 3A). Several other cytokines (IL-2, IL-3, IL-5, IL-7, GM-CSF) were not able to displace IL-13 binding (not shown). However, when IL-13Rα1 and IL-4Rα were co-expressed in CHO cells a high affinity binding site for IL-13 was reconstituted, as shown in Fig. 2B, and this high affinity IL-13 binding was fully displaced not only by IL-13 but also by IL-4 (Fig. 3B). Co-expression of the IL-13Rα1 and IL-4Rα did not change the affinity of the IL-4 receptor for IL-4 (not shown) but allowed displacement of labelled IL-4 by IL-13 (Fig. 3C). These results show that both receptor chains interact in the cell membrane to reconstitute a receptor complex that displays high affinity for IL-13 and that is shared by both IL-13 and IL-4.

3.3. Biological activity

To examine whether IL-13Rα1 is able to transduce a signal to the cell we analyzed the activation of Stat6 because this regulator of gene transcription is activated by IL-13 and IL-4 [17]. Stable transfectants expressing IL-13Rα1 either alone or in combination with IL-4Rα were stimulated with IL-13 or IL-4 and the nuclear extracts were analyzed for binding to an oligonucleotide probe containing the Cε Stat response element from the Cε human control region [18]. The results (Fig. 4) showed that no activation was detected in non-transfected CHO cells incubated with IL-4 or IL-13. Similar negative results were observed on IL-4 or IL-13 stimulation of CHO cells expressing either IL-4Rα or IL-13Rα1. However, in CHO cells expressing both chains, IL-4Rα and IL-13Rα1, stimulation with IL-4 or IL-13 clearly resulted in a binding activity to the oligonucleotide probe in the nuclear extracts. The presence of Stat6 in the complexes was confirmed by supershifting experiments as described in Section 2 (not shown).

4. Discussion

We describe here the cloning and characterization of the human IL-13Rα1. The protein, homologous to the IL-13 binding protein recently cloned from murine tissue (IL-13Rα1) [14], recognizes IL-13 with much lower affinity than the other IL-13 binding protein cloned from human cells (IL-13Rα2) [15]. IL-13 binding to CHO cells expressing hIL-13Rα1 cannot be displaced by IL-4. Co-expression of IL-4Rα with IL-13Rα1 resulted in the reconstitution of a receptor complex that bound IL-13 with higher affinity than the IL-13Rα1 alone, and that allowed cross-competition between IL-

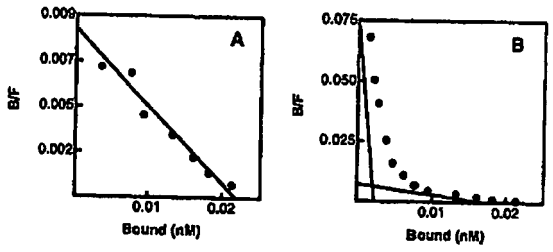

Fig. 2. Characterization of the recombinant IL-13Rα1 expressed in CHO cells. Scatchard analysis of the [^{125}I]IL-13 saturation curve with cells expressing (A) IL-13Rα1, which indicated the presence of ~26 000 sites/cell with a K_d of 4.5 ± 0.5 nM and (B) IL-13Rα1 and IL-4Rα, which indicated the presence of ~4000 sites/cell with a K_d of 32 ± 8 pM and of ~20 000 sites/cell with a K_d of 4.2 ± 1.4 nM.

13 and IL-4 as previously described for the murine IL-13Rα1 [14]. The experiments of activation of Stat6, as assayed by its property to bind to a specific sequence from the Cε promoter, complete and extend the binding results. IL-13Rα1 by itself is not capable of transducing a signal either for IL-13 or for IL-4, but when co-expressed with IL-4Rα it is capable of reconstituting a receptor complex that is able to transduce a signal for both cytokines. It should be noted that CHO cells expressing only IL-4Rα do not respond to IL-4 as measured by Stat6 activation. Since CHO cells do not express γc (unpublished results), the results are in line with previous reports that indicated the need for γc for the reconstitution of a functional IL-4 receptor [20]. The activation of Stat6 by IL-4 in cells co-expressing IL-4Rα and IL-13Rα1 clearly show that IL-13Rα1 can replace γc for the reconstitution of an active IL-4 receptor. The fact that IL-13Rα1 can replace γc for the reconstitution of an active IL-4 receptor explains, as previously suggested [6], the conflicting reports describing the need for γc for an active IL-4 receptor [9,20], and the description of active IL-4 receptors in the absence of γc [21,22]. Since the cytoplasmic domain of IL-13Rα1 is 26 amino acids shorter than that of γc we are currently investigating whether IL-13Rα1 contributes to the recruitment of Jak3, as described for γc [23], and/or to other signaling events as recently suggested [24]. In this context, it is important to emphasize the presence in the IL-13Rα1 of a proline-rich motif located in the cytoplasmic region near the transmembrane domain suggesting that IL-13Rα1 can associate with some kinases of the Jak family [25]. Together, these results show that IL-13Rα1 and IL-4Rα are sufficient to reconstitute a functional receptor for IL-13 and IL-4, and they do not exclude the possibility that other protein(s) may be associated in some cell types with the natural IL-4/IL-13 receptor complex as recently described for γc [24,26]. Two recent reports describe the homodimerization of IL-4Rα and, as a result, the intracellular signaling that finally leads to Stat6 activation. In both reports chimeric receptors were used in which the cytoplasmic and transmembrane domains of IL-4Rα were fused to the extracellular domain of the erythropoietin receptor [27] and γc [28], and dimerization was induced either with erythropoietin or with a monoclonal antibody. The apparent contradiction of these reports with our observation that CHO cells expressing IL-4Rα alone do not respond to IL-4 may indicate that if two IL-4Rα cytoplasmic domains are brought together they are able to transduce a signal to the cell, but that IL-4 does not

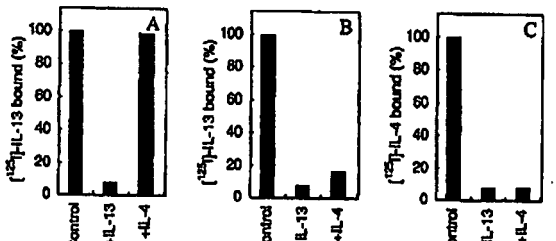

Fig. 3. Cross-competition of IL-13 and IL-4 on CHO cells expressing IL-13Rα1 alone or with IL-4Rα. A: Displacement of labelled IL-13 to cells expressing IL-13Rα1 by IL-13 (20 nM) and IL-4 (20 nM). B: Displacement of labelled IL-13 by IL-13 (20 nM) and IL-4 (20 nM) on cells expressing IL-13Rα1 and IL-4Rα. C: Displacement of labelled IL-4 by IL-13 (20 nM) and IL-4 (20 nM) on cells expressing IL-13Rα1 and IL-4Rα.

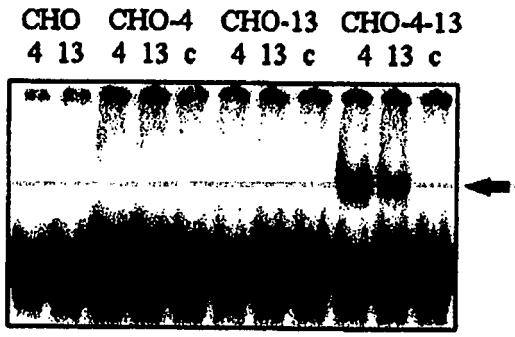

Fig. 4. Signal transduction of IL-13 and IL-4 in CHO cells expressing IL-13Rα1 alone or with IL-4Rα. The different cell lines, CHO, CHO expresssing IL-4Rα (CHO-4), IL-13Rα1 (CHO-13), and IL-4Rα and IL-13Rα1 (CHO-4-13) were incubated in the absence (c) or in the presence of 5 nM of IL-4 (4) or IL-13 (13) as indicated and then the nuclear extracts were analyzed for Stat6 activation as described in Section 2.

induce dimerization of natural IL-4Rα. In line with this hypothesis are the results of Hoffman et al. who showed that IL-4 forms a 1:1 complex with the soluble portion of IL-4Rα [29]. Alternatively, the dimerization and activation of IL-4Rα by IL-4 may depend on the density of the receptor in the cell membrane, and/or on the presence of other subunit(s) of the receptor complex that are absent in CHO cells.

In conclusion, our results demonstrate that IL-13Rα1 and IL-4Rα in the absence of γc are sufficient for the reconstitution of an active IL-13 and IL-4 receptor. The availability of the human IL-13Rα1 and IL-4Rα should allow the design of experiments to better assess the stoichiometry and the role played by each protein, and the relationship with γc and human IL-13Rα2, in the functional IL-4/IL-13 receptor complex.

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